

# Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial

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Received 8 March 2021; revised 13 April 2021; accepted 18 May 2021; online publish-ahead-of-print 9 June 2021

## Aims

Sodium–glucose co-transporter 2 (SGLT2) inhibitors, originally developed as glucose-lowering agents, have been shown to reduce heart failure hospitalizations in patients with type 2 diabetes without established heart failure, and in patients with heart failure with and without diabetes. Their role in patients with heart failure with preserved and mildly reduced ejection fraction remains unknown.

## Methods

Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) is an international, multicentre, parallel group, event-driven, randomized, double-blind trial in patients with chronic heart failure and left ventricular ejection fraction (LVEF) >40%, comparing the effect of dapagliflozin 10 mg once daily, vs. placebo, in addition to standard of care. Patients with or without diabetes, with signs and symptoms of heart failure, a LVEF >40%, elevation in natriuretic peptides and evidence of structural heart disease are eligible. The primary endpoint is time-to-first cardiovascular death or worsening heart failure event (heart failure hospitalization or urgent heart failure visit), and will be assessed in dual primary analyses – the full population and in those with LVEF <60%. The study is event-driven and will target 1117 primary events. A total of 6263 patients have been randomized.

## Conclusions

DELIVER will determine the efficacy and safety of the SGLT2 inhibitor dapagliflozin, added to conventional therapy, in patients with heart failure and preserved and mildly reduced ejection fraction.

## Keywords

Heart failure with preserved ejection fraction • Sodium–glucose co-transporter 2 inhibitors

## Introduction

Sodium–glucose co-transporter 2 (SGLT2) inhibitors, originally developed as glucose-lowering agents, have been shown to reduce heart failure hospitalizations in patients with type 2 diabetes, including those without established heart failure.<sup>1–3</sup> Moreover, in

patients with heart failure and reduced left ventricular ejection fraction (LVEF  $\leq$ 40%; HFrEF), including those with and without type 2 diabetes, both dapagliflozin and empagliflozin reduced cardiovascular death or heart failure events when added to standard therapy.<sup>4,5</sup> While the mechanisms by which SGLT2 inhibitors improve outcomes in heart failure continue to be

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investigated, they are postulated to include favourable effects on haemodynamics,<sup>6,7</sup> improvement in myocardial energetics and loading conditions, favourable effects on endothelial function and inflammation, and slowing of the progression of kidney disease.<sup>8</sup> These effects may collectively underlie observed early and sustained improvements in filling pressures and ventricular remodeling.<sup>7,9–11</sup>

Patients with preserved or mildly reduced ejection fraction (LVEF >40%) now represent the majority of those with heart failure, and experience a comparable burden of poor outcomes, such as death, hospitalizations and symptom burden, as those with LVEF ≤40%; yet suffer from dearth of effective therapies. Therefore, there is a large and urgent unmet clinical need for efficacious and safe treatments in this vulnerable patient group. Whether the benefits of SGLT2 inhibitors observed in HFrEF extend to patients with heart failure and LVEF >40% remains unknown. The benefit of dapagliflozin in DAPA-HF was similar throughout the ejection fraction spectrum under 40%,<sup>12</sup> and data from two trials of a combined SGLT1 and 2 inhibitor, including one that enrolled recently hospitalized patients with diabetes and heart failure, suggest potential benefits in people with LVEF >40%.<sup>13,14</sup> Nevertheless, most heart failure therapies that have proven effective in patients with LVEF <40% have been ineffective or significantly less effective in those with higher LVEF, with several studies showing some attenuation of benefit as LVEF rose into the normal range.<sup>15–18</sup> The heterogeneity of the heart failure with preserved ejection fraction (HFpEF) syndrome has emerged as a key hypothesis underlying the inability to identify treatments that reduce its morbidity and mortality. While HFrEF is also a heterogeneous disorder, it has proven to respond to therapies in a more homogeneous fashion, with multiple drug classes associated with improvements in morbidity and mortality. Many of these benefits appear to extend to heart failure with mildly reduced LVEF (40–50%, HFmrEF) but not for LVEF >50%. However, there is reason to believe that SGLT2 inhibitors may be beneficial in a broad spectrum of HFpEF despite the heterogeneous nature of the HFpEF syndrome. Congestion and impaired renal function are hallmarks of all types of heart failure, including HFpEF, and appear to be ameliorated by SGLT2 inhibitors. In addition, chronic kidney disease is a major risk factor for adverse outcomes in HFpEF; therefore, it is very possible that by improving kidney function, SGLT2 inhibitors may have beneficial effects across the range of LVEF. SGLT2 inhibitors also appear to improve diastolic function, reduce visceral fat (including epicardial fat), reduce arterial stiffness, and have favourable effects on endothelial function and inflammation, all of which are important mechanisms of HFpEF pathogenesis.

The Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) trial is testing the hypothesis that the SGLT2 inhibitor dapagliflozin will reduce cardiovascular death and heart failure hospitalization in patients with heart failure with a LVEF >40% (HFpEF and HFmrEF). The design of DELIVER takes into account many of the learnings from prior trials in heart failure with LVEF >40% and, along with DAPA-HF, will provide evidence for the efficacy of dapagliflozin across the full spectrum of LVEF in patients with heart failure.

## Trial design and methods

### Overall study design and governance

DELIVER is an international, multicentre, parallel group, event-driven, randomized, double-blind trial in patients with chronic heart failure and LVEF >40%, comparing the effect of dapagliflozin 10 mg once daily, vs. placebo, in addition to standard of care. The overall study design is summarized in *Figure 1*. DELIVER was designed jointly by the academic steering committee in conjunction with the sponsor. The conduct of the trial is overseen by the academic executive committee and the sponsor in conjunction with national lead investigators. The trial is registered as ClinicalTrials.gov Identifier: NCT03619213.

### Patients

The eligibility criteria for DELIVER are summarized in *Table 1*. Briefly, patients with or without diabetes were required to be 40 years of age or older, with an LVEF >40% (documented by echocardiography or cardiac magnetic resonance imaging within the last 12 months prior to enrolment without a subsequent event that might lower LVEF), evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy), and elevation in natriuretic peptides [N-terminal pro B-type natriuretic peptide (NT-proBNP) ≥300 pg/mL (≥600 pg/mL for patients in atrial fibrillation or flutter)]. Both ambulatory and hospitalized patients were eligible for enrolment.

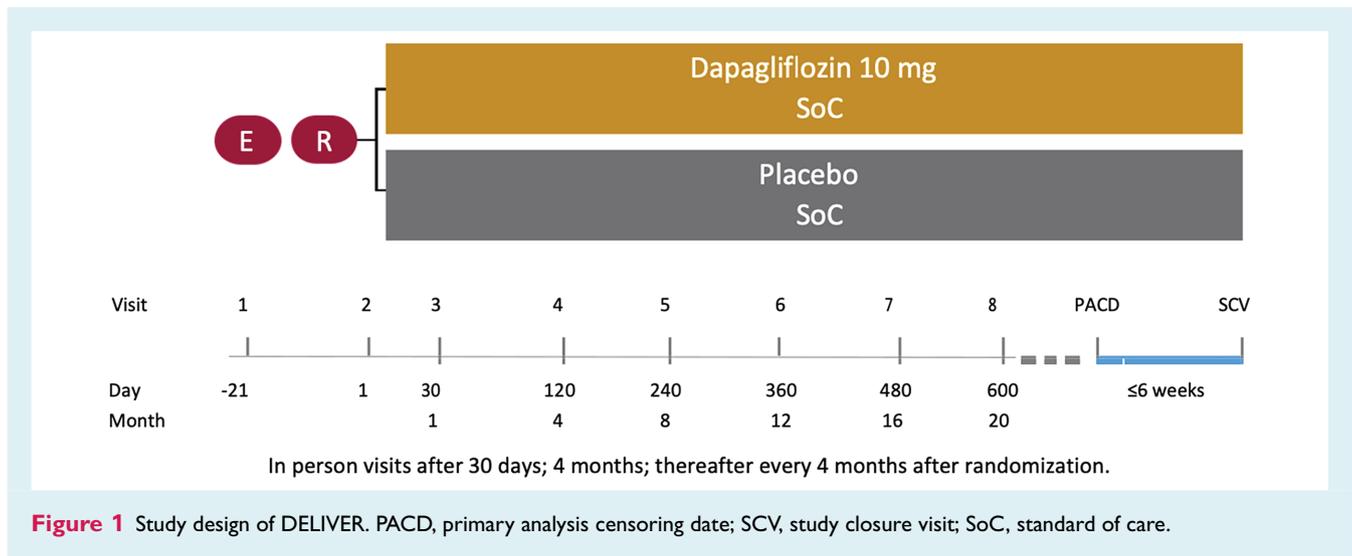
Key exclusion criteria included receiving an SGLT2 inhibitor within 4 weeks prior to randomization, or previous intolerance to SGLT2 inhibitors; type 1 diabetes; estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m<sup>2</sup> at screening; systolic blood pressure ≥160 mmHg if not on three or more antihypertensive medications, or ≥180 mmHg regardless of number of medications; probable alternative diagnoses that might account for the patients' symptoms (e.g. anaemia, hypothyroidism, primary pulmonary hypertension, chronic thromboembolic disease, requirement for home oxygen therapy); uncorrected primary valvular disease; known infiltrative heart disease, including known or suspected amyloid heart disease; myo- or pericarditis; or hypertrophic cardiomyopathy.

Enrolment in DELIVER began on 27 August 2018 following approval by appropriate ethics boards, and written informed consent was obtained from all patients enrolled in DELIVER. The last patient was randomized on 18 January 2021. Patients are enrolled at 353 sites, in 20 countries in most major geographic regions (online supplementary *Table S1*). The study is being conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

### Study procedures

#### Randomization and capping

Following informed consent and screening, and once a patient has fulfilled the criteria for randomization, all patients were centrally assigned to randomized investigational product (IP) using an interactive voice/web response system (IxRS). Randomization to IP was performed in balanced blocks to ensure approximate balance between the treatment groups (1:1). Randomization was stratified in the IxRS system based on whether the patient was or was not known to have type 2 diabetes at the time of randomization (based on either an established diagnosis or glycated haemoglobin ≥6.5% at enrolment). Patients were randomized in a 1:1 fashion to dapagliflozin 10 mg or matching placebo once daily. Several factors, including LVEF value, New



York Heart Association (NYHA) class, 'subacute' status (randomized in-hospital or within 30 days after discharge), and atrial fibrillation were monitored to enable capped randomization in the IxRS to avoid over or under-representation of these patient subgroups in each country.

### Concomitant medications

Patients are treated according to regional standard of care for all comorbidities, including diabetes and hypertension, with the exception of concomitant use of an SGLT2 inhibitor, which is not allowed by protocol.

### Study visits and monitoring

Following randomization, study visits occur at or around days 30, 120, 240, 360, and 480 after randomization, and then every 120 days thereafter. Unscheduled visits can also be performed if considered appropriate in the opinion of the investigator. The full schedule of assessments is shown in online supplementary Table S2. Treatment adherence is assessed by asking patients to return all unused investigational product and empty packages to the clinic at site visits, and non-compliant patients are counselled on the importance of taking study medication.

## Study outcomes

### Primary and other outcomes

The primary objective is to determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of worsening heart failure episodes (either unplanned hospitalization or urgent heart failure visit requiring intravenous therapy but not requiring a hospital admission) or cardiovascular death, analysed as time-to-first event (Table 2). The primary endpoint will be assessed in both the full population and in patients with LVEF <60% (dual primary analyses; see statistical analysis below). Secondary objectives are to determine whether dapagliflozin is superior to placebo in reducing the total number of heart failure events (hospitalization for heart failure or urgent heart failure visit) and cardiovascular death in (i) the full study population, and (ii) the sub-population with LVEF <60%; in improving patient-reported outcomes measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS);

in reducing cardiovascular death; in reducing all-cause mortality. Several exploratory endpoints will also be assessed (online supplementary Table S3): whether dapagliflozin compared with placebo will have an effect on slope of eGFR (assessed as between randomization and 1 and 2 years, respectively, and between a post-randomization time point and 1 and 2 years, respectively); and assessment of benefits within the sub-domains of the KCCQ, stratified by type 2 diabetes status at randomization, and adjusted for the baseline value.

### Endpoint adjudication

An independent Cardiovascular Endpoint Committee (CEC), blinded to treatment assignment, is categorizing all deaths and adjudicating non-fatal cardiovascular events as possible endpoints based on the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials developed by the Standardized Data Collection for Cardiovascular Trials Initiative.<sup>19</sup> All potential episodes of possible ketoacidosis are also being adjudicated.

### Accommodation for COVID-19

As the COVID-19 pandemic evolved during the course of the study, the trial has made several adaptations to ensure the quality and integrity of the data collected. These included as necessary conversion of in-person visits to phone and virtual visits, remote data collection for patient-reported outcomes, reporting of all COVID-19 related adverse events and adjudication of COVID-19 related hospitalizations and deaths.

## Statistical considerations

### Sample size considerations and statistical analyses

The primary objective of the study is to determine the superiority of dapagliflozin vs. placebo added to standard of care in reducing the composite of worsening heart failure events (hospitalization for heart failure or urgent heart failure visit) or cardiovascular death, measured as time-to-first occurrence of any of the components of the composite. Two hypotheses will be tested simultaneously (i.e. dual primary analyses) for the primary analysis: (i) in the full population and (ii) in the population with LVEF <60%. Alpha will be allocated to

**Table 1** Eligibility criteria for DELIVER**Inclusion criteria**

1. Ability to give written informed consent.
2. Men and women age  $\geq 40$  years.
3. Documented diagnosis of symptomatic heart failure (NYHA class II–IV) at enrolment, and a medical history of typical symptoms/signs of heart failure  $\geq 6$  weeks before enrolment with at least intermittent need for diuretic treatment (requiring recurrent intermittent dosing).
4. LVEF  $> 40\%$  and evidence of structural heart disease (i.e. left ventricular hypertrophy or left atrial enlargement) documented by the most recent echocardiogram, and/or cardiac magnetic resonance within the last 12 months prior to enrolment. For patients with prior acute cardiac events or procedures that may reduce LVEF, e.g. as defined in exclusion criterion, qualifying cardiac imaging assessment at least 12 weeks following the procedure/event is required. Structural heart disease will be defined as:
  - LA enlargement with at least one of the following: LA width (diameter)  $\geq 3.8$  cm or LA length  $\geq 5.0$  cm, or LA area  $\geq 20$  cm, or LA volume  $\geq 55$  mL or LA volume index  $\geq 29$  mL/m.
  - Left ventricular hypertrophy with septal thickness or posterior wall thickness  $\geq 1.1$  cm.
5. NT-proBNP  $\geq 300$  pg/mL at Visit 1 for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at Visit 1, NT-proBNP must be  $\geq 600$  pg/mL.
6. Patients may be ambulatory, or hospitalized; patients must be off intravenous heart failure therapy (including diuretics) for at least 12 h prior to enrolment and 24 h prior to randomization.

**Exclusion criteria**

1. Receiving therapy with an SGLT2 inhibitor within 4 weeks prior to randomization or previous intolerance to an SGLT2 inhibitor.
2. Type 1 diabetes mellitus.
3. eGFR  $< 25$  mL/min/1.73 m<sup>2</sup> (CKD-EPI formula) at Visit 1.
4. Systolic blood pressure  $< 95$  mmHg on two consecutive measurements at 5 min intervals, at Visit 1 or at Visit 2.
5. Systolic blood pressure  $\geq 160$  mmHg if not on treatment with  $\geq 3$  blood pressure lowering medications or  $\geq 180$  mmHg irrespective of treatments, on two consecutive measurements at 5 min intervals, at Visit 1 or at Visit 2.
6. Myocardial infarction, unstable angina, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial flutter/fibrillation, valve repair/replacement within 12 weeks prior to enrolment. Before enrolment, these patients must have their qualifying echocardiography and/or cardiac magnetic resonance examination at least 12 weeks after the event.
7. Planned coronary revascularization, ablation of atrial flutter/fibrillation and valve repair/replacement.
8. Stroke or transient ischaemic attack within 12 weeks prior to enrolment.
9. Probable alternative or concomitant diagnoses which in the opinion of the investigator could account for the patient's heart failure symptoms and signs (e.g. anaemia, hypothyroidism).
10. Body mass index  $> 50$  kg/m<sup>2</sup>.
11. Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD (i.e. requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalization for exacerbation of COPD requiring ventilatory assistance within 12 months prior to enrolment).
12. Previous cardiac transplantation, or complex congenital heart disease. Planned cardiac resynchronization therapy.
13. Heart failure due to any of the following: known infiltrative cardiomyopathy (e.g. amyloid, sarcoid, lymphoma, endomyocardial fibrosis), active myocarditis, constrictive pericarditis, cardiac tamponade, known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, or uncorrected primary valvular disease.
14. A life expectancy of less than 2 years due to any non-cardiovascular condition, based on investigator's clinical judgement.
15. Inability of the patient, in the opinion of the investigator, to understand and/or comply with study medications, procedures and/or follow-up or any conditions that, in the opinion of the investigator, may render the patient unable to complete the study.
16. Active malignancy requiring treatment (with the exception of basal cell or squamous cell carcinomas of the skin).
17. Acute or chronic liver disease with severe impairment of liver function (e.g. ascites, oesophageal varices, coagulopathy).
18. Women of child-bearing potential (i.e. those who are not chemically or surgically sterilized or post-menopausal) not willing to use a medically accepted method of contraception considered reliable in the judgement of the investigator or who have a positive pregnancy test at randomisation or who are breast-feeding.
19. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study site).
20. Previous randomization in the present study.
21. Participation in another clinical study with an investigational product or device during the last month prior to enrolment.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LA, left atrial; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium–glucose co-transporter 2.

**Table 2** Primary and secondary study objectives and endpoints

Study objective	Corresponding endpoint
<p><b>Primary objective</b></p> <p>To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalization for HF or urgent HF visit) in patients with HF and preserved systolic function in (i) the full study population, and (ii) the sub-population with LVEF &lt;60%</p>	<p>Time to the first occurrence<sup>a</sup> of any of the components of this composite:</p> <ol style="list-style-type: none"> <li>1. CV death</li> <li>2. Hospitalization for HF</li> <li>3. Urgent HF visit (e.g. emergency department or outpatient visit)</li> </ol>
<p><b>Secondary objectives</b></p> <p>To determine whether dapagliflozin is superior to placebo in reducing the total number of HF events (hospitalization for HF or urgent HF visit) and CV death in (i) the full study population, and (ii) the sub-population with LVEF &lt;60%</p> <p>To determine whether dapagliflozin is superior to placebo in improving patient-reported outcomes measured by KCCQ</p> <p>To determine whether dapagliflozin is superior to placebo in reducing CV death</p> <p>To determine whether dapagliflozin is superior to placebo in reducing all-cause mortality</p>	<p>Total number<sup>b</sup> of HF events (first and recurrent) and CV death</p> <p>Change from baseline in the total symptom score of the KCCQ at 8 months</p> <p>Time to the occurrence of CV death</p> <p>Time to the occurrence of death from any cause</p>
<p><b>Safety objective</b></p> <p>To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF</p>	<p>Serious AEs, AEs leading to treatment discontinuation, amputations, AEs leading to amputation and potential risk factor for AEs leading to amputations affecting the lower limbs</p>

AE, adverse event; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction.

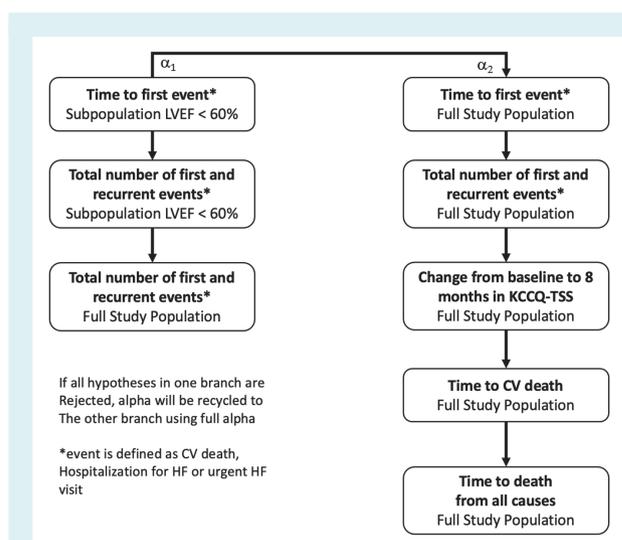
<sup>a</sup>Analysis using Cox regression stratified by type 2 diabetes at baseline.

<sup>b</sup>Analysis performed using the semi-parametric method of Lin, Wei, Yang and Ying (LWYY).

each primary test to ensure control of the overall type I error rate, with the exact alpha split determined prior to the interim analysis. The study protocol was modified on 12 November 2020 introducing the current dual primary analysis, in which cardiovascular death or worsening heart failure events will be evaluated in both the full study population (as original primary analysis) and the population with LVEF <60%. For the original analysis, 844 primary events were targeted to provide 90% power for the primary endpoint. To allow for testing the dual primary hypotheses, the target number of patients with a primary endpoint was subsequently increased to 1117 to provide adequate statistical power for each of the two dual primary analyses. The original targeted sample size of 4700 patients was increased to 6100 based on blinded monitoring of event accrual and the increase in target number of primary events. It is anticipated that at least 70% of the primary endpoint events (i.e. approximately 780 events) will be contributed by the LVEF <60% sub-population. A total sample size of 6100 patients is anticipated to provide 93% power to detect a 20% relative risk reduction for the primary endpoint for a two-sided nominal alpha of 0.024. Recruitment was completed on 21 January 2021 with a total of 6263 patients randomized. The anticipated median follow-up will be 27 months. All analyses will be according to the intention-to-treat principle. Full details of all analyses will be provided in a statistical analysis plan prior to unblinding of the trial.

### Methods of statistical analysis

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints will be utilized. Statistical significance will be assessed in two branches in the pre-specified order of the endpoints and populations as specified in Figure 2. Following the



**Figure 2** Hierarchical testing scheme for primary and secondary endpoints. CV, cardiovascular; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; LVEF, left ventricular ejection fraction.

dual assessment of the primary endpoint (time-to-first event for the composite endpoint of cardiovascular death and worsening heart failure event) in both the full population, and in those with LVEF <60%, subsequent testing will occur in two parallel paths as shown. If the null

hypothesis is rejected in the full population for the primary analysis analysed using a Cox proportional hazards model, then testing will occur for recurrent events in the full population using the LWYY method, followed by comparison of change from baseline to 8 months in the KCCQ-TSS using the rank ANCOVA method (to test difference in distribution) and the win ratio test (to estimate treatment effect), followed by comparison of time to cardiovascular death, followed by time to all-cause death in Cox regression analyses. If the null hypothesis is rejected in the sub-population with LVEF <60%, total and recurrent events will be assessed first in the sub-population and subsequently in the full population, with allocation of alpha for each successive positive test. If all null hypotheses are rejected within a particular branch, the alpha is recycled to the other branch where the hypotheses will be tested with full alpha.

### Analysis of secondary endpoints

Sub-domains of the KCCQ-TSS (symptom frequency and symptom burden) and overall symptom score (OSS) will be analysed with rank ANCOVA and win ratio in the same manner as for TSS. Descriptive statistics of scores and changes from baseline will be presented for all scores.

### Subgroup analyses

The following pre-specified sub-groups of interest will be assessed for the dual primary endpoints: age at vs. below, vs. above, the median; sex; race; geographic region; NYHA class (II vs. III/IV) at enrolment; LVEF category at enrolment (41–49% vs. 50–59%, and ≥60%); NT-proBNP at enrolment (at or below, vs. above the median); randomization in hospital or within 30 days of discharge vs. others; eGFR at enrolment (<60 vs. ≥60 mL/min/1.73 m<sup>2</sup>); body mass index at enrolment (<30 vs. ≥30 kg/m<sup>2</sup>); diabetes status at enrolment; systolic blood pressure at randomization (at or below vs. above the median); atrial fibrillation or flutter vs. other rhythms at enrolment. The effect of treatment will also be assessed as a function of LVEF and glycated haemoglobin examined as continuous variables.

In addition to the within trial analyses, we have pre-specified prior to the unblinding of DAPA-HF that data from both dapagliflozin heart failure trials, DAPA-HF and DELIVER, will be pooled and assessed in a patient-level meta-analysis to assess the effect of dapagliflozin across the full spectrum of heart failure.

### Data monitoring committee and interim analysis

A data safety monitoring committee is overseeing the trial and will undertake one interim analysis when approximately 67% of the target number of primary endpoints are reached, where the primary composite endpoint will be tested in the full study population at a significance level of 0.2%. If the null hypothesis is rejected, superiority of dapagliflozin to placebo on cardiovascular death will be tested at the same significance level.

## Discussion

Heart failure with LVEF >40% (HFpEF and HFmrEF) represents a large group of patients without clear guideline-directed therapy with great unmet need. SGLT2 inhibitors are the first treatments being tested for heart failure with LVEF >40% that are not neurohormonal modulators. This might give this class an advantage over previously tested agents for both efficacy and

safety. While vasodilator-type agents clearly benefit patients with HFpEF, peripheral vasodilatation may provide less benefit and may be associated with more hypotension in patients with higher LVEF. On the other hand, several of the mechanisms by which SGLT2 inhibitors have been postulated to be beneficial in HFpEF would be expected to be similarly beneficial in patients with heart failure and higher LVEF, such as improvements in filling pressures and ventricular remodelling,<sup>9,10,11</sup> and kidney benefits.<sup>8</sup> Furthermore, SGLT2 inhibitors have been shown to improve diastolic function in patients with diabetes and LVEF ≥50%,<sup>20</sup> reduce obesity and attenuate epicardial fat accumulation or its secretion of deleterious adipokines,<sup>21</sup> as well as improve endothelial function and reduce inflammation – mechanistic factors particularly associated with heart failure in the setting of higher LVEF. Indeed, we observed no heterogeneity in the treatment response to dapagliflozin based on LVEF in patients with HFpEF, and more recent data from SOLOIST-WHF and SCORED suggest that therapy with sotagliflozin benefited recently hospitalized patients with HFpEF.<sup>13,14</sup>

Clinical trials in HFpEF have been challenging for several reasons, including difficulties in ensuring enrolment of the appropriate patients who truly have the clinical syndrome of heart failure, and because of the phenotypic, biological and likely therapeutic heterogeneity of the disease. All prior outcomes trials in this population to date have fallen short of demonstrating a convincing therapeutic benefit on their primary endpoint. Most recently, the PARAGON-HF trial, which compared sacubitril/valsartan to valsartan, narrowly missed statistical significance for the primary endpoint of total heart failure hospitalizations and cardiovascular death.<sup>17</sup> However, the data from PARAGON-HF suggested that patients with LVEF at or below the pre-specified median of 57% had a greater treatment benefit than those with higher LVEF, and this finding was confirmed when LVEF was assessed continuously. This pattern of declining benefit with increasing LVEF has also been observed in two other clinical trials, TOPCAT which compared spironolactone to placebo, and CHARM-Preserved which compared candesartan to placebo.<sup>15,16</sup> Whether declining benefit with increasing LVEF is unique to these prior treatment approaches that utilized neurohormonal modulators or is in fact a general characteristic of patients with heart failure with LVEF >40%, is unknown. That prior HFpEF trials have shown that treatment effect with a broad range of therapies declined with increasing LVEF provided the rationale for the dual primary analysis incorporated into DELIVER.

The design of DELIVER is unique in several ways. First, DELIVER was designed to complement DAPA-HF which assessed the efficacy of dapagliflozin in patients with HFpEF. The results of both studies will be pooled to assess the effects of dapagliflozin across the spectrum of ejection fraction. The entry criteria reflected the contemporary view that patients with heart failure should have both elevation of natriuretic peptides and evidence of structural heart disease (Table 3).<sup>17,22–26</sup> In contrast to the PARAGON-HF and TOPCAT trials which were restricted to patients with LVEF ≥45% who had never had LVEF <40%, DELIVER is enrolling patients with LVEF >40%, and is allowing patients with previous LVEF ≤40%. This will allow for a wide range of patients with

**Table 3 Comparison of DELIVER and other trials in heart failure with left ventricular ejection fraction >40%**

	CHARM-Preserved <sup>22</sup>	PEP-CHF <sup>23</sup>	I-PRESERVE <sup>24</sup>	TOPCAT <sup>25</sup>	PARAGON-HF <sup>17</sup>	EMPEROR-Preserved <sup>26</sup>	DELIVER
Patients, n	3023	850	4128	3445	4800	5988	6200
Treatment arms	Candesartan vs. placebo	Perindopril vs. placebo	Irbesartan vs. placebo	Spironolactone vs. placebo	Sacubitril/valsartan vs. valsartan	Empagliflozin vs. placebo	Dapagliflozin vs. placebo
Key inclusion criteria	NYHA class II–IV, prior CV hospitalization	Clinical diagnosis of DHF with ≥ signs/symptoms of HF, ≥ 2 of the following: LAE/LVH/impaired left ventricular filling/AF	NYHA class II–IV + any corroborating evidence (e.g. HF sign), LVH or LAE considered optional	≥ 1 HF symptom + ≥ 1 HF sign, elevated NP or HFH	NYHA class II–IV, elevated NT-proBNP (adjusted for AF and higher if no recent HF hospitalization), structural heart disease (LAE or LVH)	NYHA class II–IV, elevated NT-proBNP	NYHA class II–IV, elevated NT-proBNP (adjusted for AF), structural heart disease (LAE or LVH)
LVEF cutpoint	>40%	>40%	≥45%	≥45%	≥45%	>40%	>40%
Endpoint	First of either CV death or HFH	First of either all-cause death of HFH	First of either all-cause death or hospitalization for a CV cause	First of either CV death, HFH, or RSD	CV death and total HFH (first and recurrent)	CV death or HFH	CV death or HFH either in the full population or in patients with LVEF <60%

AF, atrial fibrillation; CV, cardiovascular; DHF, diastolic heart failure; HF, heart failure; HFH, heart failure hospitalization; LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

mildly reduced ejection fraction. Second, the primary outcome will incorporate both heart failure hospitalizations and urgent heart failure visits. Urgent heart failure visits, requiring evidence of intravenous diuretic therapy, have been a component of the primary endpoint of several prior heart failure trials, including DAPA-HF, and have proven to be both prognostically similar to heart failure hospitalizations and similarly discriminative of treatment effects in several trials.<sup>27,28</sup> Moreover, with increasing needs for outpatient management of worsening heart failure due to changes in healthcare care delivery and patient preferences, urgent heart failure visits are logical for inclusion in the primary endpoint.

While prior studies in this population with neurohormonal modulators have noted decline in efficacy with increasing LVEF, the unique mechanism of action of SGLT2 inhibitors and data from DECLARE-TIMI 58 and DAPA-CKD suggest the potential for beneficial effects across the spectrum of ejection fraction.<sup>3,29</sup>

Nevertheless, the incorporation in DELIVER of dual-primary analyses with appropriate protection against multiple comparisons allows for the possibility of differential effect by LVEF, while preserving adequate statistical power to assess both the overall study population.

While the primary outcomes in DELIVER are based on time-to-first event for cardiovascular death or heart failure event, which includes both heart failure hospitalizations and urgent heart failure visits, testing hierarchy for secondary endpoints allows for assessment of first and recurrent events in both the sub-population of patients with LVEF <60% and then the full population (if the null hypothesis for the sub-population is rejected) for the primary outcome. Recurrent events have provided more statistical power in some, but not all, trials in heart failure,<sup>30,31</sup> and may be especially helpful in trials of HFpEF where there are relatively few cardiovascular deaths relative to heart failure events. Furthermore, if the null hypotheses are rejected for each of these endpoints (primary for LVEF <60%, recurrent events for LVEF <60%, and recurrent events for the full population), the full population can then be re-tested with full alpha. This unique approach takes into account the uncertainty regarding which population will have the greatest benefit and which testing method (time to first vs. recurrent events) would be most successful in this population and with this therapy. The specific order of the hierarchy, with assessment of KCCQ-TSS above cardiovascular and all-cause mortality, is based on the importance of the endpoints to the population, the relatively low number of deaths in this population, and the low overall likelihood of benefit for fatal endpoints.

There are both similarities and differences between DELIVER and EMPEROR-Preserved,<sup>32</sup> the other ongoing SGLT2 inhibitor outcome trial in a similar population. Both studies have similar entry criteria, including patients with heart failure and LVEF >40%, requirement for elevation in natriuretic peptides, and evidence for structural heart disease (although patients could be enrolled in EMPEROR-Preserved without evidence of structural heart disease if they had a heart failure hospitalization within 12 months). The primary differences are that the dual primary endpoints in DELIVER allow for the possibility of testing the primary efficacy hypothesis in both the full population and in the subset of patients with LVEF <60%, an innovation that takes into account the

results of prior trials. In addition, other trials, including EMPUSLE (NCT04157751)<sup>33</sup> and DAPA ACT HF-TIMI 68 (NCT04363697) are testing SGLT2 inhibitors in acute and stabilized hospitalized heart failure patients.

In summary, DELIVER will determine whether dapagliflozin compared with placebo will reduce the risk of cardiovascular death or worsening heart failure in patients with HFpEF or HFmrEF. DELIVER will provide complementary information to DAPA-HF, which studied the adjacent population with HFrEF. The design of DELIVER takes into account the collective experience from prior trials in a patient population with great unmet need.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

## Funding

The DELIVER study was funded by AstraZeneca.

**Conflict of interest:** All authors have received research funding in the form of grants to institution from AstraZeneca and/or consulting to AstraZeneca.

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